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(54) Title: HEPATOCYTE NUCLEAR FACTOR 4 α MODULATOR COMPOUNDS

(57) Abstract: The present invention is directed to hepatocyte nuclear factor 4 α (HNF-4 α) receptor modulator compounds. This invention is also directed to pharmaceutical compositions containing such compounds as well as methods of using such compounds and pharmaceutical compositions for modulating HNF-4 α receptors as well as processes mediated by HNF-4 α receptors. Also provided are methods of making such compounds and pharmaceutical compositions, as well as intermediates used in their synthesis.

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31/385, 31/35, 31/075, C07D 311/04, 335/04, 215/00,
215/16, C07C 41/00

(74) Agents: **SEIDMAN, Stephanie, L.** et al.; Fish & Richardson P.C., 12390 El Camino Real, San Diego, CA 92130 (US).

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/22907

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/47,31/385,31/35,31/075; C07D 311/04,335/04,215/00,215/16; C07C 41/00

US CL : 514/434,456,311,717; 546/152,178; 549/23,434; 568/632

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/434,456,311,717; 546/152,178; 549/23,434; 568/632

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- A	US 5,015,658 A (CHANDRARATNA) 14 May 1991 (14.05.1991), column 13 line 63 recites species.	1,8,15,23,30,38 ----- 2-7,9-14,16-22,24-29,31-37,39-114
X -- A	US 6,391,287 B1 (BALDO et al) 21 May 2002 (21.05.2002), column 4 lines 27-67 exemplify several species	1,8,15,23,30,38 ----- 2-7,9-14,16-22,24-29,31-37,39-114

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

19 April 2005 (19.04.2005)

Date of mailing of the international search report

25 MAY 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

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PATENT COOPERATION TREATY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference		Date of mailing (day/month/year)
18202-022WO1		25 MAY 2005
FOR FURTHER ACTION See paragraph 2 below		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US04/22907	16 July 2004 (16.07.2004)	16 July 2003 (16.07.2003)
International Patent Classification (IPC) or both national classification and IPC		
IPC(7): A61K 31/47,31/385,31/35,31/075; C07D 311/04,335/04,215/00,215/16; C07C 41/00 and US Cl.: 514/434,456,311,717; 546/152,178; 549/23,434; 568/632		
Applicant		
LIGAND PHARMACEUTICALS, INC		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Amelia A. Owens Telephone No. 571-272-0700
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/22907

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US04/22907**Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)

Claims 1,8,15,23,30,38 YESClaims 2-7,9-14,16-22,24-29,31-37,39-114 NO

Inventive step (IS)

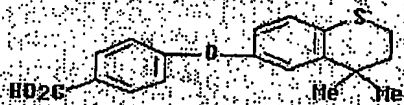
Claims 1,8,15,23,30,38 YESClaims 2-7,9-14,16-22,24-29,31-37,39-114 NO

Industrial applicability (IA)

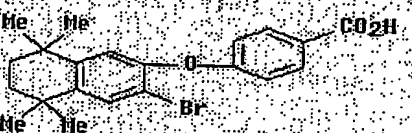
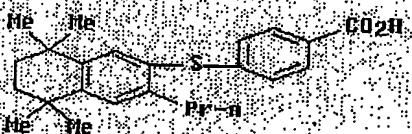
Claims 1-114 YESClaims NONE NO

2. Citations and explanations:

Claims 1,8,15,23,30,38 lack novelty under PCT Article 33(2) as being anticipated by Chandraratna USP 5,015,658. the compounds are pharmaceuticals.



Claims 1,8,15,23,30,38 lack novelty under PCT Article 33(2) as being anticipated by Baldo et al USP 6,391,287 B1. A few of the species are listed below, although the reference teaches several. The compounds are cosmetic compositions.



Claims 1-114 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.